Evidence that the association of childhood trauma with psychosis and related psychopathology is not explained by gene-environment correlation: A monozygotic twin differences approach

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ABSTRACT

Background: Converging evidence supports childhood trauma as possible causal risk for psychosis and related psychopathology. However, studies have shown that baseline psychotic symptoms may actually increase risk for subsequent victimization, suggesting that exposure to CT is not random but may result from pre-existing vulnerability. Therefore, studies testing whether the association between CT and psychopathology persists when accounting for gene-environment correlation are much needed.
Methods: A monozygotic (MZ) twin differences approach was used to examine whether differences in CT exposure among MZ twin pairs would be associated with MZ differences in symptoms. As MZ twins are genetically identical, within-pair correlations between CT exposure and psychopathology rule out the possibility that the association is solely attributable to gene-environment correlation. 266 monozygotic twins (133 pairs) from a larger general population study were available for analysis.
Results: CT was associated with symptoms of psychosis ($B = 0.62$; $SE = 0.08$, $p < .001$) and overall psychopathology ($B = 43.13$; $SE = 6.27$; $p < .001$). There were measurable differences within pairs in CT exposure and symptoms, allowing for meaningful within-pair differences. Within-pair differences in CT exposure were associated with within-pair differences in symptoms of psychosis ($B = 0.35$; $SE = 0.16$; $p = .024$), as well as with overall psychopathology ($B = 29.22$; $SE = 12.24$; $p = .018$), anxiety ($B = 0.65$; $SE = 0.21$; $p = .002$) and depression ($B = 0.37$; $SE = 0.18$; $p = .043$).
Conclusion: While it is not unlikely that pre-existing vulnerability may increase the risk for traumatic exposures, such gene-environment correlation does not explain away the association between CT and psychopathology. The present findings thus suggest that at least part of the association between CT and psychopathology may be causal.

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1. Introduction

Converging evidence suggests that childhood trauma (CT) – and especially the intentional infliction of harm by others – may be a risk factor for psychosis (Arseneault et al., 2011; Moriyama et al., 2018; Van Nierop et al., 2014) A meta-analysis by Varese and colleagues estimated a 3-fold increase in risk for psychosis after exposure to childhood traumatic events (Varese et al., 2012).

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While the relationship between childhood trauma as a risk factor, and psychosis is well established, the question of causality remains. Before such a conclusion can be substantiated, a number of issues need to be addressed (Kelleher et al., 2013). For example, the temporality of the relationship is hard to establish. Only a few studies have been able to demonstrate a prospective association. One study showed that adolescents and adults that were sexually abused before the age of 16 years were at a 2-fold increased risk for developing a diagnosis of any psychotic disorder and a 2.6-fold increased risk for schizophrenia compared with age- and gender-matched non-abused control subjects (Cutajar et al., 2010). Similar findings were found at the level of later psychotic experiences (Arseneault et al., 2011). Yet, the issue with both studies is that they did not examine whether psychotic experiences were already present at the time of exposure, or not (Van Winkel et al., 2013). The two most methodologically rigorous studies so far prospectively examined psychotic experiences and exposure to adverse events in childhood and adolescents between (Kelleher et al., 2013; Schaefer et al., 2017). These studies found a bidirectional relationship between childhood trauma and psychosis, with trauma predicting psychotic experiences over time, but also the other way around, with psychotic experiences predicting subsequent exposure to traumatic events such as being bullied or being physically assaulted.

The finding of an association between psychotic experiences and later exposure to traumatic events points to the necessity to consider other (non-causal) explanations in the relationship between childhood trauma and psychosis. One such explanation is that the exposure to traumatic events, especially when inflicted by others, is not random but may result from a pre-existing vulnerability, such as genetic vulnerability. In agreement with this hypothesis, a large study of patients with a psychotic disorder, their unaffected siblings and healthy controls showed a gradient of exposure to childhood trauma, with highest levels of exposure in patients, intermediate levels in the unaffected siblings and lowest levels in healthy controls (Heins et al., 2011). This may suggest that genetic vulnerability is not only expressed at the symptom level, but may also lead to an increased risk for victimization, a phenomenon also referred to as gene-environment correlation (Van Winkel et al., 2013). Thus, if gene-environment correlation is present, the association between childhood trauma and psychosis may not be causal but the mere manifestation of underlying genetic risk.

While it is clear that this is a crucial issue, only a few studies so far investigated whether the association between childhood trauma and psychosis is still present when controlling for the possibility of gene-environment correlation (Alemany et al., 2013; Fisher et al., 2011; Schaefer et al., 2017; Trotta et al., 2016, 2015). Two studies used family psychiatric history as proxy for genetic risk, and a third used a polygenic risk score for schizophrenia (PRS), but found no support for passive gene-environment correlation (Fisher et al., 2014; Trotta et al., 2016, 2015). A limitation of these studies, however, is that neither familiar risk nor polygenic risk is currently able to capture all relevant genetic risk. To overcome this limitation, Alemany et al. (2013) used a monozygotic (MZ) twin differences approach to examine this issue in 85 MZ twin pairs. The reasoning behind this design is that if absolute differences in environmental exposure (between MZ twins) are associated with absolute differences in psychosis expression, this would show that the association cannot be attributed to underlying genetic risk, since monozygotic twins share 100% of their genes. In their paper, the authors indeed found that greater differences in trauma exposure among MZ twins were associated with (more) psychotic symptoms, thus supporting childhood trauma as a true risk factor for psychosis. Interestingly, in a recently published longitudinal study, Schaefer et al. (2017) used a similar approach in a larger sample ($N_{pairs} = 579$) across a wider psychiatric spectrum, and found comparable results. In the present study, we aimed to replicate these findings.

An important further consideration is that childhood trauma is not specifically associated with psychosis. In a meta-analysis by Matheson et al. (2013), the authors showed that the association of childhood trauma with schizophrenia was comparable to its association with some of the other major psychiatric disorders, such as affective psychosis, depression, dissociative disorders, posttraumatic stress disorder, and personality disorders. Moreover, rather than specifically developing psychotic symptoms, recent work suggests that childhood trauma victims typically show comorbid psychotic, anxiety, and depression symptoms. This pattern was evident in the general population, and in samples with a primary diagnosis of a psychotic disorder, depression or an anxiety disorder (van Nierop et al., 2017, 2015). In their large scale prospective study, Schaefer et al. (2017) similarly showed that victimization predicted increased liability to multiple psychiatric spectra. Therefore, the present paper did not only analyze psychotic symptoms but also aimed to extend the MZ twin differences approach to symptoms of depression and anxiety as well as overall psychopathology. We hypothesized that larger absolute differences in childhood trauma exposure among MZ twins would be associated with greater differences in the absolute expression of psychosis, depressive symptoms, anxiety symptoms and overall psychopathology.

2. Methods

2.1. Sample

Monozygotic twin-pairs were selected from the TwinssCan study. In 2010, adolescents and young adult twins were recruited from the East Flanders Prospective Twin Survey (EFPTS; Derom et al., 2013) through a newsletter asking them to participate in a longitudinal study. 839 individuals participated in the baseline assessment. Of those 292 were MZ-twins, 486 DZ-twins, 18 were part of a triplet and 43 were non-twin siblings. A total of 363 parents participated. The Medical Ethics Review Committee at the university hospital KU Leuven approved the study. All participants signed informed consents; parents gave written informed consent in case participants were under the age of 18. Participants were between the ages of 14–34 years ($M = 17.42$; $SD = 3.55$). 59.71% of the participants were female ($N = 501$).

Zygosity was determined through sequential analysis based on sex, fetal membranes, umbilical cord blood groups, placental alkaline phosphatase, and DNA fingerprints. Twins with at least one different genetic marker were classified as dizygotic; monochorionic twins were classified as monozygotic. Participants were included if they understood the study procedure and were able to provide valid, reliable and complete data. They were excluded if they had a pervasive mental disorder as indicated by caregivers. Full reports of the sample are reported elsewhere (Loos et al., 1998; www.twins.be).

2.2. Measures

2.2.1. Childhood trauma

Childhood trauma was assessed with the Dutch translation of the short version of the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1997). The CTQ is comprised of five subscales: sexual abuse, emotional abuse, physical abuse, physical neglect, and emotional neglect. Participants were asked to rate 28-items on a scale from 1 'never' to 5 'always'. Seven items were recoded so that a lower score means less trauma exposure and vice versa, according to the scoring manual (Bernstein et al., 1997). Consequently, a continuous variable was constructed based on the mean-score of each participant across all five domains.

2.2.2. Symptoms

To assess psychotic symptoms and other psychopathology the Symptom Checklist 90 (SCL-90; Derogatis et al., 1976) was used. This self-report questionnaire consists of 90-items rated on a 5-point scale ranging from 'not at all' to 'very much'. Participants were asked to rate to what extent they were bothered by each item in the past week. It comprises nine dimensions (psychoticism, paranoia, anxiety,

depression, somatization, obsessive-compulsive, interpersonal sensitivity, hostility, phobic anxiety). A global severity score was computed (i.e. mean score across all items) (Holi, 2003), as well as mean scores of the subscales of interest: psychosis (mean of psychoticism (10 items) and paranoia (6 items)), anxiety (10 items) and depression (13 items). The 9-factor structure of the SCL-90 was used to compute a total score and total scores for each of the three subscales.

2.3. Analyses

To analyze whether differences in exposure to childhood trauma were associated with differences in symptom outcomes, irrespective of genetic predisposition, within-pair differences values were computed (for a review see Carlin et al., 2005). In order for the within-pair differences not to cancel each other out, we generated an 'absolute differences' variable where all paired-differences were transformed into positive values. Paired-difference values were computed for the CTQ, SCL-90 global score and three SCL-90 subscales used. Multiple regression analyzes were performed, first to examine whether the association between childhood trauma and symptoms was significant for the whole sample, followed by examining whether within-pair differences were associated with symptom differences. To account for the skewness of the data 'censored regression analyses' were performed (Tobin, 1958). Censored regression models allow for the estimation of the relationship between one or more predictor variables and some outcome variable of interest when there is either left and/or right censoring in the outcome variable. In particular, the model coefficients indicate how unit changes in the predictor variables are related to changes on a latent continuum, which is only observed in censored form via the outcome variable. Censoring can occur, for example, when using measurement instruments with detection limits. In the present study, left- censoring is occurring due to a number of participants with a score of zero for the SCL-90 assessment.

3. Results

3.1. Sample

Of the 146 MZ twin pairs that were eligible, 133 pairs had complete data on the CTQ, SCL-90 for both twins. The other 13 pairs were excluded as difference scores could not be computed without both twins having valid data. A description of the sample can be found in Table 1.

3.2. Psychopathology

In a first step, we found that exposure to childhood trauma in the whole sample was associated with psychosis ($B = 0.62$; $SE = 0.08$, $p < .001$). Second, exposure to CT was also associated with overall symptoms of psychopathology ($B = 43.13$; $SE = 6.27$; $p < .001$), symptoms of anxiety ($B = 0.56$, $SE = 0.10$, $p < .001$) and depression ($B = 0.62$, $SE = 0.10$, $p < .001$).

Within-pair differences in childhood trauma ranged between 0 and 1.48 on a 0–5 scale ($M = 0.23$, $SD = 0.23$). Within-pair differences in overall psychopathology ranged between 0 and 216 on a 0–450 scale ($M = 29.24$, $SD = 33.01$). Differences in within-pair symptoms of psychosis ranged from 0 to 2.4 ($M = 0.33$, $SD = 0.37$), anxiety from 0 to 3.2 ($M = 0.38$, $SD = 0.48$), and depression from 0 to 3 ($M = 0.44$, $SD = 0.48$), both on a 0–5 scale.

As hypothesized, within-pair differences in CT were associated with within-pair differences in psychotic symptoms ($B = 0.35$; $SE = 0.16$; $p = .024$), as well as overall psychopathology ($B = 29.22$; $SE = 12.24$; $p = .018$). Moreover, within-pair difference in CT exposure were also associated with within-pair difference in symptoms of anxiety ($B = 0.65$; $SE = 0.21$; $p = .002$) and depression ($B = 0.37$; $SE = 0.18$; $p = .043$). No gender differences were found ($B = -0.54$, $SE = 0.52$, $p = .301$), indicating that the effect sizes were similar for males and females.

Table 1
Sociodemographic characteristics of the final sample.

	MZ-twins ($N = 266$)
Age	Range: 14–34 years
	$M = 18.22$ ($SD = 4.35$)
Female gender	64.66% ($n = 172$)
Treatment for psychiatric symptoms (lifetime)	
Without medication	3.76% ($n = 10$)
With medication	3.00% ($n = 8$)
Treatment + medication	4.51% ($n = 12$)
Income/not in	
No (own) income	84.58% ($n = 225$)
Income from regular work	13.91% ($n = 37$)
Unemployment benefits	0.37% ($n = 1$)
Social employment money	0.37% ($n = 1$)
Scholarship	0.37% ($n = 1$)
Living situation	
Alone	1.13% ($n = 3$)
Partner/own family	7.14% ($n = 19$)
Living with parents/family	83.08% ($n = 221$)
Housemates	7.51% ($n = 20$)
Other	0.75% ($n = 2$)
Educational performance	
Much better than average	6.77% ($n = 18$)
Better than average	36.46% ($n = 97$)
Average	47.37% ($n = 126$)
Less than average	3.01% ($n = 8$)

Note: educational performance was measured by asking participants to indicate their educational performance based on their grades.

4. Discussion

This study provided evidence for, and advanced the current literature on the relationship between childhood trauma (CT) and psychosis, using a monozygotic (MZ) twin differences approach. The results concurred with our hypothesis that larger absolute differences in childhood trauma exposure among MZ twins would be associated with greater differences in absolute expression of psychotic, depressive, anxiety symptoms and overall psychopathology. The present findings suggest that the association of CT with psychosis and related psychopathology is genuine and is not accounted for by mere gene-environment correlation.

4.1. The question of causality

It is generally assumed that childhood trauma is a causal factor in bringing on later psychosis. Many of the findings related to childhood trauma and psychosis indeed seem to be compatible with a causal explanation. First, the association is robust, strong, and consistent across samples, as demonstrated by a meta-analysis (Varese et al., 2012). Second, the same meta-analysis also showed a clear dose-response relationship. Third, previous work has also shown a temporal relationship between CT exposure and later psychosis, although this work also showed a bidirectional relationship (Kelleher et al., 2013). The current results add to the latter findings by suggesting that, while we cannot rule out that gene-environment correlation plays a role, at least part of the association of CT with psychosis and related psychopathology is genuine, in agreement with a possible causal explanation. In other words, while a pre-existing vulnerability might increase the risk for exposure to traumatic events, traumatic events on their own explain at least part of the variation in the development of psychopathology.

4.2. Childhood trauma as 'unspecific risk factor'

In agreement with previous studies, our findings support the association between childhood traumatic experiences and symptoms of psychosis in the general population (Alemany et al., 2013; Arseneault et al., 2011; Janssen et al., 2004; Kelleher et al., 2013; Schaefer et al., 2017; Spauwen et al., 2006; Van Nierop et al., 2014; Wigman et al.,

2011). Moreover, we were able to replicate findings by Alemany et al. (2013) in that we found differences in trauma exposure between MZ twins to be associated with differences in psychotic symptoms. Our study extended these results by also looking at differences in symptoms of anxiety, depression and overall psychopathology. The results indicated an association between CT and symptoms of depression and anxiety, as well as overall psychopathology. We found that more CT exposure (differences) was associated with more symptoms (differences). The current study supports the notion that CT is not specifically associated with one or another disorder, but may be an unspecific risk factor, or even a specific risk factor for comorbid psychopathology (Matheson et al., 2013; van Nierop et al., 2017, 2015). These findings may suggest that studying CT in relation to a specific disorder may not be the most fruitful approach; rather, the entire myriad of comorbid symptoms may need to be taken into account (Van Winkel, 2015).

4.3. Strengths and limitations

The current results should be interpreted in light of some strengths and limitations. Because we used a MZ twin differences approach, shared environmental and genetic influences could be controlled for, and the results can be interpreted as in that at least part of the association between CT and psychosis, anxiety, depression, and general psychopathology, is genuine. We were able to replicate the findings by Alemany et al. (2013) with a larger sample. Nevertheless, there were some limitations. Reports of trauma exposure were retrospective which may induce recall-bias. However, previous studies indicated that retrospective reports of childhood trauma are reliable, even in individuals with mental illness (Fisher et al., 2011), and retrospective reports are more likely to be an underestimation of prevalence rather than an overestimation (Hardt and Rutter, 2004). Also, psychopathology was assessed over the past week, which may have resulted in an underestimation of the level of psychopathology. However, any underestimation of symptom levels would have resulted in a reduced likelihood to find an association rather than create spurious findings. Further, psychopathology was assessed by self-report rather than by a trained clinical professional. However, the psychometric properties of the instrument are high and indicate good validity and reliability (Franke, 2002). Lastly, while the MZ twin differences approach is able to successfully control for genetic risk, other unmeasured non-genetic factors shared between the MZ twins could still potentially play a role in the association between childhood trauma and psychopathology reported in the present manuscript.

5. Conclusion

In the present study we explored whether differences in childhood trauma among MZ twins were associated with within-pair differences in symptoms of psychosis, anxiety, depression and overall psychopathology. The present findings suggest that, while it is not unlikely that pre-existing vulnerability may increase the risk for traumatic exposures, the association between CT and symptoms of psychopathology cannot be solely attributed to gene-environment correlation. More research is needed to better understand under which circumstances childhood trauma increases the risk for later mental health problems.

Contributors

RvW, JD, MDH, CD, NJ, CM-L, JvO, ET, BPR and MW designed the study and wrote the protocol. AL and RvW managed the literature searches and analyses. AL and RvW undertook the statistical analysis, and author AL wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors report no conflict of interest.

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